1,128,044

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

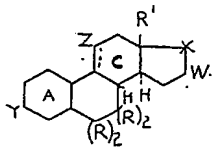
13-(C_{2-5})Alkyl-11-Oxygenated Gonenes

I, HERCHEL SMITH, of 500 Chestnut Lane, Wayne, Delaware County, Pennsylvania, United States of America, of British nationality, do hereby declare the invention for which I pray that a patent may be granted to me and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 13 - alkyl - 11 - oxygenated steroids and to processes for making such steroids.

The term "gonane" used hereinafter refers to the unsubstituted tetracyclic cyclopentanohydrophenanthrene nucleus. In the normal configuration of the gonane nucleus, the hydrogen atoms appearing at the 8- 10- and 13- positions possess what is designated as the β-configuration, i.e. they extend in a direction above the average plane of the tetracyclic ring system, and hydrogen atoms present at the 9- and 14- positions possess what is designated as the α-configuration, i.e. they extend in a direction below the plane of the ring system.

The compounds of the invention are 13 - (C_{2-5})alkyl - 3,11,17 - trioxygenated - unsaturated - gonanes, having the structure

I 

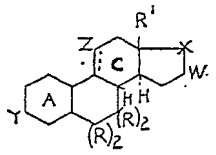
where R^1 is a C_{2-5} alkyl group, X is a carbonyl, hydroxymethylene, ketalised carbonyl or esterified hydroxymethylene group, Z is an oxo, hydroxy, ketalised oxo, or etherified or esterified hydroxy group, W is hydrogen, a hydroxy group or an esterified hydroxy group, R is hydrogen or one or more C_{1-6} alkyl groups at one or both of positions 6 and 7 (which may be the same or different) and Y is a hydroxy or esterified or etherified hydroxy group and ring A is aromatic or Y is an etherified hydroxy group and ring A contains the 2,5(10) - diene system or Y is a hydroxy, acyloxy or oxo group and ring A contains a 4 or 5(10) double bond; and ring C can be saturated in which case the hydrogen atom at the 9- position is in the α-configuration or it can contain a 9(11) double bond when Z is an acyloxy group; or a D-homo analogue thereof. The group Z may be a hydroxy group esterified with an acid such as acetic acid, propionic acid, valeric acid, caproic acid, phenylpropionic acid, cyclopentyl - propionic acid, or benzoic acid.

Similarly the group X can be an acyloxymethylene group, for example an acetoxymethylene or benzoyloxymethylene group. The group Y can be an acetoxy or benzoyloxy group or an alkoxy group, for example a methoxy group. The group W can be an acetoxy group.

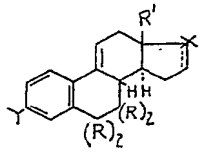
The compounds of the invention, in general, are high melting white crystalline solids and are generally soluble in solvents such as benzene, ether and ethyl acetate.

[*Price 4s. 6d.*]

Compounds of the invention of structure (I)

I 

where R^1 is a C_{2-5} alkyl group, X is a carbonyl, hydroxymethylene or esterified hydroxymethylene group, Z is an oxo, hydroxy, ketalised oxo, or etherified or esterified hydroxy group, W is hydrogen, a hydroxy group or an esterified hydroxy group, R is hydrogen or one or more C_{1-6} alkyl groups at one or both of positions 6 and 7 (which may be the same or different) and Y is a hydroxy or esterified or etherified hydroxy group and ring A is aromatic or Y is an etherified hydroxy group and ring A contains the 2,5(10) - diene system or Y is an oxo group and ring A contains a 4 or 5(10) double bond; and ring C can be saturated in which case the hydrogen atom at the 9-position is in the α-configuration or it can contain a 9(11) double bond when Z is an acyloxy group; or a D - homo analogue thereof, can be prepared by hydroborating a compound of structure (II)

II 

where R, R^1 and X are as defined above, Y is a hydroxy or etherified or esterified hydroxy group and there can be an ethylenic bond at the 16-position in the D-ring, or the D-homo analogue of structure II and if desired

(i) the product of hydroboration is Birch reduced to give a 2,5(10)-diene,

(ii) the Birch reduction product is hydrolysed to give a compound where ring A has a 4 or 5(10) double bond and a 3-keto group,

(iii) an 11- or 16- or 17 - hydroxy group is oxidised to a corresponding keto group,

(iv) an 11 - keto group is reduced to an 11β - hydroxy group or is ketalized or

(v) an 11- or 16- or 17 - hydroxy group is esterified.

Preferably hydroboration is achieved by the use of diborane, followed by hydrogen peroxide in the presence of an alkali.

In this specification the term "hydroboration" is defined as the two-stage process in which a steroid containing a double bond is reacted with a boron hydride such as diborane to give a steroid - boron complex with is then treated with an oxidising agent such as alkaline hydrogen peroxide to introduce a hydroxy group into the steroid molecule. The introduction to the double bond of the hydroxy group and a hydrogen atom is generally a *cis* - addition, and, in 13 - polycarbon alkyl steroids, the addition is normally *trans* to the substituent at the 13-position.

Referring now to Figure I, the sequence of reactions involved in the synthesis of one of the compounds of the invention, namely 13 - ethylgona - 1,3,5(10) - triene-3,11α,17β - triol (III), is illustrated.

FIG I

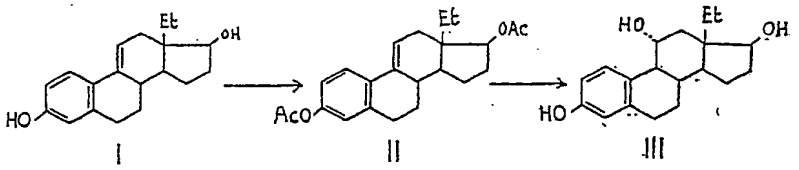
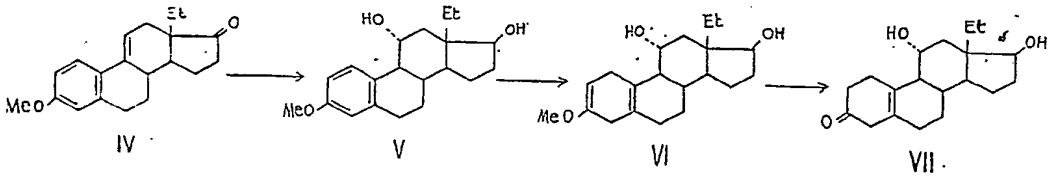


FIG 2



13 - Ethylgona - 1,3,5(10),9(11) - tetraene - 3,17β - diol (I) is dissolved in acetic anhydride and pyridine, and heated at about 100° for about an hour. The solvents are removed by distillation under reduced pressure and the residue crystallised to obtain the diacetate, 13 - ethyl - 3,17β - diacetoxygona - 1,3,5(10), 9(11) - tetraene (II). This diacetate is dissolved in dry tetrahydrofuran and treated with excess diborane, generated by adding a solution of sodium borohydride in diglyme to a solution of boron trifluoride etherate in diglyme. The reaction mixture is maintained at room temperature for a period of a few hours and then water is cautiously added to decompose the excess diborane. Hydrogen peroxide and aqueous sodium hydroxide are added and the mixture is refluxed for about 1 half hour. After evaporation of solvent and acidification with hydrochloric acid, the product (III) is isolated by means of conventional acid-base extraction procedures and recrystallisation from methanol at $-5°$.

Suitable solvents for the hydroboration reaction are ethers, and include tetrahydrofuran, diethyl ether, and diglyme (the dimethyl ether of diethyleneglycol).

The diborane reactant can be passed into the reaction vessel by means of a gas inlet tube or generated *in situ*. The latter alternative is accomplished by the use of one of the alkali metal borohydrides or aluminium hydrides in conjunction with a reagent such as aluminium trichloride, boron trifluoride, or boron trichloride. A preferred combination is sodium borohydride and boron trifluoride etherate, dissolved in diglyme.

Referring now to Figure 2, the sequence of reactions involved in the synthesis of another compound of the invention, namely 13 - ethyl - 11α,17β - dihydroxygon - 5(10) - en - 3 - one (VII), is illustrated. 13 - Ethyl - 3 - methoxygona - 1,3,5(10), 9(11) - tetraen - 17 - one (IV), dissolved in tetrahydrofuran, is treated with diborane, and the resulting organoborane oxidised with alkaline peroxide. Conventional work-up and recrystallisation from ether yield 13 - ethyl - 3 - methoxygona - 1,3,5(10) - triene-11α,17β - diol (V). Reduction of the aromatic A-ring with an alkali metal and alcohol in liquid ammonia (Birch reduction) results in the formation of 13 - ethyl - 3 - methoxygona - 2,5 - (10) - diene - 11α,17β - diol (VI). The product (VIII) is then obtained by hydrolysis with a weak acid such as as oxalic acid or acetic acid. Hydrolysis with a strong mineral acid such as hydrochloric acid results in the formation of the corresponding gon - 4 - en - 3 - one.

It is clear that the 11α - hydroxy - 13 - (C_{2-5})alkyl gonenes of the invention can be subjected to a variety of conventional reactions. For example, the 11α - hydroxy group can be oxidised to a keto group by means of chromic acid. Subsequent reduction with a conventional reagent such as lithium aluminium hydride or sodium borohydride reduces the keto group to a β - hydroxy group. Thus 11β - hydroxy compounds are made available. The hydroxy group at the 17-position can similarly be oxidised.

Any of the hydroxy groups on the gonane nucleus can be esterified. Acetylation by means of acetic anhydride is readily accomplished. Benzoyl derivatives are prepared by treatment of the alcoholic group with benzoyl chloride. Among the other esterifications that can be performed are those utilising as acids propionic acid, valeric acid, caproic acid, phenylpropionic acid or cyclopentylpropionic acid.

The hydroboration reaction is best performed on 13 - (C_{2-5}) alkyl gonenes which do not possess an active hydrogen atom. Such an active hydrogen atom, if present, would react rapidly with diborane by extraction of a hydride ion therefrom. For this reason the 3 - hydroxy group which may be present on the starting material for the hydroboration reaction is preferably protected by esterification or etherification. It can be an alkoxy or acyloxy group, or a cyclopentyloxy or cyclohexyloxy group.

It is also clear that there can be other variants in the starting materials which result in 11α - hydroxygonatrienes or gonenes bearing the corresponding variants. For example, there can be at the 6 or 7 positions a C_{1-6} alkyl group such as methyl, or ethyl. By utilising as starting materials 13 - (C_{2-5})alkyl - 6- or 7 - C_{1-6} alkyl - gona-1,3,5(10),9(11) - tetraenes, and subjecting them to the hydroboration and oxidation sequence, there are formed 13 - (C_{2-5})alkyl-6 or -7-C_{1-6} alkyl - 11α - hydroxygona-trienes, which can be further treated to yield 13 - (C_{2-5})alkyl - 6- or 7 - $C1_{-6}$ alkyl-11α - hydroxygon - 4 - en - 3 - ones or gon - 5(10) - en - 3 - ones. The C_{2-5} alkyl group at the 13-position can be an ethyl, propyl, isopropyl, butyl or pentyl group. Instead of the normal 5 - membered D-ring, there can be a 6-membered homologated D-ring. It is thus apparent that by using as a starting material the appropriate gona-1,3,5(10),9(11) - tetraene, there can be produced 11α - hydroxy - gona - 1,3,5(10) - trienes, 11α - hydroxygon - 4 - en - 3 - ones and 11α - hydroxygon - 5(10) - en - 3-ones having any of the above-mentioned variations.

If the hydroboration reaction is performed using a 13 - (C_{2-5})alkyl - gona - 1,3,5(10),9(11),16 - pentaene, reaction occurs at the 16-position as well as at the 11-position. Subsequent oxidation results in the formation of 13 - ethyl compounds having hydroxy groups at the 11- and 16- positions.

The 13 - (C_{2-5}) - alkylgona - 1,3,5(10),9(11) - tetraene starting materials for the present invention are prepared by methods described in Patent Specification No. 1,024,912. Such methods comprise the acid - catalysed isomerisation of the corresponding 13 - (C_{2-5}) - alkylgona - 1,3,5(10),8 - tetraene or the ring-closure of a 13 - (C_{2-5}) - alkyl - 9,10 - secogona - 1,3,5(10) - trien - 9 - one.

The compounds of the invention are useful for preparing other steroids with hormonal activity. In addition, many of them show hormonal effects themselves, particularly activities of the metrotropic and adrenal corticoid type. For example 13 - ethylgona - 1,3,5(10) - triene - 3,11α,17β - triol shows metrotropic activity while 13 - ethyl - 11α,17β - dihydroxygon - 5(10) - en - 3 - one shows glucocorticoid activity.

The product of a total synthesis which has not included a suitable resolution stage will contain the 13β or *d* and 13α or *l* forms in equimolar mixture or racemate form. Where the configuration of groups at positions 6, 7, 11 and 16 is referred to as 11α or 16β or the like, this is with reference for nomenclature purposes to the *d*-compounds. Preferably the starting material in a process of the invention is a resolved 13β or *d*-enantiomer. The invention particularly includes the resolved *d*-compounds and the *d*-compounds in admixture with the corresponding *l*-compounds especially racemic mixtures. In the examples herein the compounds produced were racemates and are referred to as 13β-forms and the (±)- or (dl) prefix has been omitted.

The compositions of this invention are formulated for pharmaceutical use as solid capsules, tablets, suppositories, etc. by combining them with conventional carriers. Such conventional solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, dextrin, pectin, starch, gelatin, tragacanth, methylcellulose and sodium carboxymethylcellulose. Diluents, flavouring agents, solubilisers, lubricants, suspending agents, binders or tablet - disintegrating agents may be employed. Liquid preparations such as solutions, suspensions or emulsion may also be prepared. A water-propylene glycol may be used for parenteral injection. An aqueous suspension suitable for oral use can be made by utilising natural or synthetic gums, resins, methylcellulose or other well-known suspending agents.

Example 1

13 - Ethylgona - 1,3,5(10),9(11) - tetraene - 3,17β - diol (20.8 g.) in acetic anhydride (80 ml.) and pyridine (40 ml.) is maintained at 100°C for 75 minutes. The solvents are removed by evaporation *in vacuo* to obtain a red oil, which crystallised on standing. The resulting solid dissolved in benzene is filtered through Florisil (Registered Trade Mark) (a fluorosilicate adsorbent) (200 g.), and washed with benzene (2 l). The benzene is evaporated to give 13 - ethyl - 3,17β - diacetoxygona - 1,3,5(10), 9(11) - tetraene (27.5 g.). m.p. 146—147°C.

13 - Ethyl - 3,17β - diacetoxygona - 1,3,5,(10),9(11) - tetraene (22.5 g.) in dry tetrahydrofuran (250 ml.) is treated with diborane [produced by adding sodium borohydride (6 g.) in diglyme (100 ml.) to boron trifluoride etherate (42 ml.) in diglyme (66 ml.) at room temperature over a period of three hours]. The mixture is maintained at room temperature overnight and then the excess diborane is decomposed by the addition of water. Hydrogen peroxide (30%; 144 ml.) and 2.5-*N* aqueous sodium hydroxide (200 ml.) is added and the mixture is refluxed gently for 30 minutes. The tetra-

hydrofuran is evaporated *in vacuo*, the residue acidified with hydrochloric acid and extracted with ether (2×600 ml.). The ether extracts are washed with potassium bicarbonate solution and brine, and dried (Na_2SO_4). The solvent is evaporated *in vacuo* to obtain a yellow oily solid (14 g.) which is triturated with ether (50 ml.) and the resulting solid (6 g.) filtered off.

This material is recrystallised from methanol (70 ml.) at −5°C to obtain 13-ethylgona - 1,3,5(10) - triene - 3,11α,17β - triol (2.5 g.) as a white solid, m.p. 165° as a cloudy melt, clearing by 175°C. The mother liquors from the trituration and recrystallisation are combined. After evaporation of the solvents, the residue (12.2 g.) is chromatographed on Florisil (750 g.) as follows:

Eluant (Benzene-methanol)		Eluate	
Composition	Volume	Weight	Compound
19:1	500 ml.	86 mg.	An oil
19:1	1400 ml.	4.5 g.	13-Ethylgona-1,3,5(10)-triene - 3,9α,17β-triol
19:1	800 ml.	887 mg.	A mixture of alcohols
19:1	1600 ml.		13-Ethylgona - 1,3,5(10)-
9:1	1 litre)		triene-3,11α,17β-triol

The last fraction is recrystallised to give 13 - ethylgona - 1,3,5(10) - triene - 3,11α,17β - triol (3.25 g.)

EXAMPLE 2

13 - Ethylgona - 1,3,5(10) - triene - 3,11α,17β - triol (49.4 mg.) in pyridine (0.25 ml.) and acetic anhydride (0.25 ml.) is maintained at 100° for 1.5 hours. The solvents are evaporated *in vacuo* and the residue recrystallised from ethanol (2 ml.) to obtain 13 - ethyl - 3,11α,17β - triacetoxy - gona - 1,3,5(10) - triene (46 mg.) as white needles, m.p. 153.5—154.5°C. Found: C, 69.91; H, 7.60; O, 22.49%. Calculated for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53; O, 22.48.

EXAMPLE 3

13 - Ethylgona - 1,3,5(10) - triene - 3,11α,17β - triol (46.8 mg.) in warm benzoyl chloride (0.1 ml.) and pyridine (0.4 ml.) is allowed to stand for 3 days. The mixture is triturated with water (10 ml.); the solid is filtered off and recrystallised from alcohol-acetone (10:1) (30 ml.) to obtain 13 - ethyl - 3,11α,17β - tribenzoyloxygona - 1,3,5(10-triene (69.4 mg.) as fine white needles, m.p. 243—245°. Found: C, 78.40; H, 6.17%. Calculated for $C_{40}H_{38}O_6$: C, 78.15; H, 6.23%.

EXAMPLE 4

13 - Ethylgona - 1,3,5(10) - triene - 3,11α,17β - triol (1.1 g.) in 2.6*N*-sodium hydroxide (35 ml.) at 10°C is treated with benzoyl chloride (4 ml.) and shaken vigorously for 30 min. Ether (10 ml.) is added and mixture shaken for a further 5 min. The aqueous layer is extracted with ether (70 ml). The combined ether extracts are washed, dried and evaporated *in vacuo* to obtain an oil, which crystallises to give 13 - ethyl - 3-benzoyloxygona - 1,3,5(10) - triene - 11α,17β - diol (1.45 g.), m.p. 184—187.5°C which is recrystallised from benzene to give the pure compound, m.p. 191—192°C. Found: C, 77.17; H, 7.50%. Calculated for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44%.

EXAMPLE 5

13 - Ethyl - 3 - benzyloxygona - 1,3,5(10) - triene - 11α,17β - diol (431 mg.) in acetone (30 ml.) is treated dropwise with 4*N* - chromic acid in sulphuric acid [Jones reagent (half strength)] until a permanent brown colour remains in the supernatant liquid (1.25 ml. added). After standing for about 1 hr., the mixture is treated with water (50 ml.), and extracted with ether (100 ml. and then 40 ml.). The combined ether extracts are washed with aqueous potassium carbonate and brine and then dried. Evaporation yields an oil which solidifies; the solid is recrystallised from ethanol (5 ml.) to obtain 13 - ethyl - 3 - benzoyloxygona - 1,3,5(10) - triene - 11,17 - dione (198 mg.), m.p. 151.5—155°; ultraviolet absorptions at 231 mμ (ε 18,250), 272 mμ (ε 3540), and 281 mμ (ε 2200). A further recrystallisation from ethanol yields an analytical sample, m.p. 154.5—155°C. Found: C, 77.25; H, 6.33%. Calculated for $C_{26}H_{26}O_4$: 77.59; H, 6.51%.

EXAMPLE 6

13 - Ethyl - 3 - benzoyloxygona - 1,3,5(10) - triene - 11,17 - dione (86.4 mg.) in pyridine (1 ml.) and acetic anhydride (1 ml.) is refluxed for three hours. The solvents are evaporated *in vacuo* and the resulting brown oil is dissolved in ether. The solution is washed, dried and evaporated to give a residue which is crystallised from ethanol (20 ml.) to obtain 13 - ethyl - 3 - benzoyloxy - 11 - acetoxygona - 1,3,5(10),9(11) - tetraen - 17 - one (57.7 mg.) m.p. 206.5—208°C. A further recrystallisation from ethanol gives a pure sample, m.p. 208.5—209°C. Found: C, 75.48; H, 6.32%. Analysis calculated for $C_{28}H_{28}O_5$. C, 75.65; H, 6.35%.

EXAMPLE 7

13 - Ethyl - 3 - benzyloxygona - 1,3,5(10) - triene - 11,17 - dione (328 mg.) in absolute alcohol is treated with sodium borohydride (499 mg.) and the mixture refluxed for 2 hours. The solvent is evaporated *in vacuo*, the resulting white solid is treated with water (50 ml.) acidified with dilute hydrochloric acid, and extracted with ether (2×75 ml.). The combined ether extracts are washed with aqueous potassium carbonate and brine, dried, and evaporated to obtain an oily solid which is recrystallised from ethanol (5 ml.) at −5°C to obtain 13 - ethylgona - 1,3,5(10) - triene - 3,11β,17β - triol, m.p. 232—7°d. A further recrystallisation from ethanol yields an analytical sample, m.p. 237—41°. Found: C, 75.94; H, 8.9%. Calculated for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67%.

EXAMPLE 8

13 - Ethylgona - 1,3,5(10) - triene - 3,11β,17β - triol (241 mg.) in 2.13*N* aqueous sodium hydroxide (13 ml.) is treated with benzoyl chloride (1 ml.) and, after shaking vigorously for 15 minutes, the mixture is successively extracted with ether, benzene, and ethyl acetate. After evaporation of the solvents there is obtained 13 - ethyl - 3 - benzoyloxygona - 1,3,5(10) - triene - 11β,17β - diol (181 mg.) as a white solid.

EXAMPLE 9

Diborane [generated by adding sodium borohydride (5.0 g.) in diglyme (110 ml.) to boron trifluoride etherate (37.5 ml.) of diglyme (115 ml.) over a period of 2 hrs] is added to 13 - ethyl - 3 - methoxygona - 1,3,5(10),9(11) - tetraen - 17 - one (20 g.) in dry tetrahydrofuran (100 ml.). The mixture is allowed to stand for 48 hours and then water (10 ml.) is cautiously added to decompose the excess borane followed by hydrogen peroxide (30%; 115 ml.) and 2 - *N* sodium hydroxide (165 ml.). The mixture is refluxed for ½ hour, the tetrahydrofuran is evaporated *in vacuo;* the aqueous solution is extracted with ether (600 ml.), washed with brine and dried. The ether solution is evaporated to about 80 ml; on standing, a solid (9.7 g.) crystallised out and is recrystallised from ether to obtain 13 - ethyl - 3 - methoxygona - 1,3,5(10) - triene - 11α,17β-diol m.p. 165—167°C. A second crystalline form of the compound melts at 131.5—132°C. Found: C, 75.78; H, 8.63%. Analysis calculated for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%.

EXAMPLE 10

13 - Ethyl - 3 - methoxygona - 1,3,5(10) - triene - 11α,17β - diol in toluene and cyclohexanone is mixed with freshly distilled aluminium isopropoxide and the mixture refluxed under nitrogen for four hours. After cooling, a solid is filtered off and the filtrate is washed, dried and evaporated to give 13 - ethyl - 3 - methoxygona - 1,3,5(10)-triene - 11,17 - dione.

EXAMPLE 11

13 - Ethyl - 3 - methoxygona - 1,3,5(10) - triene - 11,17 - dione in ethanol is reduced with sodium borohydride by refluxing for two hours. The solvent is evaporated *in vacuo* and water is added; the mixture is acidified with dilute hydrochloric acid, and extracted with ether. The ether extracts are washed, dried and evaporated to give 13-ethyl - 3 - methoxy - gona - 1,3,5(10) - triene - 11β,17β - diol.

EXAMPLE 12

13 - Ethyl - 3 - methoxygona - 1,3,5(10) - triene - 11β,17β - diol (86 mg.) in dry tetrahydrofuran (10 ml.) and liquid ammonia (30 ml.) (distilled from sodium) is maintained at −40°C to 25°C. Lithium (326 mg) is added with stirring followed by ethanol (4.2 ml.) dropwise over a period of 35 minutes. The ammonia is allowed to evaporate at room temperature; the mixture is quenched with water, and extracted with ether (2×75 ml.), the extracts are washed, dried and evaporated to give 13 - ethyl - 3 - methoxygona - 2,5(10) - diene - 11β,17β - diol.

EXAMPLE 13

13 - Ethyl - 3 - methoxygona - 2,5(10) - diene - 11β,17β - diol (69 mg.) is stirred with concentrated hydrochloric acid (0.1 ml.), methanol (2 ml.) and water (0.054 ml.) for 2½ hr. at room temperature. Water (20 ml.) is added and the mixture extracted with ethyl acetate (2 × 75 ml.) The extracts are washed, dried and evaporated to give a product (80 mg.) which is crystallised from ethyl acetate to obtain a 13 - ethyl - 11β,17β - dihydroxygon - 4 - en - 3 - one, m.p. 197.5—198.5°C.

EXAMPLE 14

13 - Ethyl - 3 - methoxygona - 2,5(10) - diene - 11α,17β - diol (2.0 g.) in toluene (144 ml.) and cyclohexanone (40 ml.) is mixed with freshly distilled aluminium isopropoxide (2.0 g.) and the mixture is refluxed under nitrogen for 4 hr. After cooling, a yellow solid is filtered off; the filtrate is washed, dried and evaporated at 100° C/0.5 mm. to obtain 13 - ethyl - 3 - methoxygona - 2,5(10) - diene - 11,17 - dione.

EXAMPLE 15

13 - Ethyl - 3 - methoxygona - 1,3,5(10) - triene - 11α,17β - diol (252 mg.) in pyridine (2 ml.) and acetic anhydride (2 ml.) is maintained at 100°C. for 1½ hr. The solvents are evaporated *in vacuo;* the resulting oil is dissolved in benzene, and the residual oil is crystallised with ethanol (4 ml.) to obtain 13 - ethyl - 3 - methoxy - 11α,17β - diacetoxygona - 1,3,5(10) - triene, m.p. 130.5—131.5°C. Found: C, 71.72; H, 7.92%. Calculated for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05%.

EXAMPLE 16

13 - Ethyl - 3 - methoxygona - 1,3,5(10) - triene - 11α,17β - diol (7.5 g.) in dry tetrahydrofuran (200 ml.) and liquid ammonia (300 ml.) (distilled from sodium) is treated with stirring with lithium (4.73 g.); the resulting blue solution is maintained at −30-C, and is treated dropwise with ethanol (57 ml.) over a period of 1½ hr. After allowing the mixture to stand at room temperature overnight, it is quenched with water (1.5 l.) and extracted with ether (1.5 l.). The ether extract is washed with brine, dried, and evaporated to give 13 - ethyl - 3 - methoxygona - 2,5(10) -diene - 11α,17β-diol. A sample recrystallised from ethanol melted at 201—6°C.

EXAMPLE 17

13 - Ethyl - 3 - methoxygona - 2,5(10) - diene - 11α,17β - diol (4.65 g.), concentrated hydrochloric acid and water (2 ml.) are stirred at room temperature for 2½ hr. after which time all the solid has gone into solution. The solution is quenched with water (600 ml.) and the mixture extracted with ethyl acetate (250 ml.) and 400 ml.) The combined extracts are washed with brine, dried and evaporated under partial vacuum to a volume of about 50 ml. The product is allowed to crystallise at room temperature. A portion of the product (2.55 g, m.p. 206—210°C is recrystallised from ethyl acetate to obtain an analytical sample of 13 - ethyl - 11α,17β - dihydroxygon-4 - en - 3 - one, m.p. 214—217°; ultraviolet absorption at 241 mμ (ε 13,700). Found: C, 74.56; H, 9.52%. Calculated for $C_{19}H_{28}O_3$. C, 74.96; H, 9.27%.

EXAMPLE 18

13 - Ethyl - 11α,17β - dihydroxygon - 4 - en - 3 - one (953 mg.) in warm Analar acetone (100 ml.) is cooled to 15° and treated dropwise with stirring, with a 10% excess of 4 *N* chromic acid in sulphuric acid (3.5 ml.) and water (Jones reagent, half strength). The mixture is maintained at room temperature for 10 min., treated with water (200 ml.), the acetone evaporated at room temperature *in vacuo* and the oily product extracted with ether. The ether extracts are washed with aqueous potassium bicarbonate and brine, dried and evaporated to obtain a residue (793 mg.) which is crystallise from ethanol (5 ml.) to obtain 13-ethylgon-4-ene-3,11,17 - trione (558 mg.) m.p. 163.5—165°C, ultraviolet absorption at 239 mμ (ε 14,450).

EXAMPLE 19

13 - Ethyl - 3 - methoxygona - 2,5(10) - diene - 11α,17β - diol (109 mg.) methanol (7.3 mg.), water (1.3 ml.) and oxalic acid dihydrate (130 mg.) is stirred for 2½ hr., during which time complete solution is attained. Wster (50 ml.) is added and the mixture extracted with ether (2 × 40 ml.). The ether extracts are washed with brine and dried; the solution is evaporated to give a white product (97 mg.) which is recrystallised from ethyl acetate (5 ml.) to obtain 13 - ethyl - 11α,17β - dihydroxygon - 5(10) - en - 3 - one (46 mg.), m.p. 207—212°C. Found: C, 74.68; H, 9.19%. Calculated for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27%.

EXAMPLE 20

13 - Ethyl - 3 - acetoxygona - 1,3,5(10),9(11) - tetraen - 17 - one (2.04 g.) in isopropenylacetate (50 ml.) is mixed with *p* - toluenesulphonic acid (600 mg.) and is heated on a steam bath. Portions (2 × 3 ml.) of solvent are removed by distillation after two and four hours and the mixture is maintained at 100° overnight. The volume is reduced to about 20 ml. by slow distillation through a short column over a period of six hours under a pressure of about 600 mm. Ether (70 ml.) is added and the resulting solution is washed with aqueous potassium bicarbonate and brine, and dried. The solvent is evaporated to obtain a red oil (2.37 g.) which is dissolved in benzene and chromatographed on Florisil (150 g.)

Eluent	Eluate
Benzene (990 ml.)	colourless oil (252 mg.)
Benzene (2 litre)	pale yellow solid (1.17 g.)
Benzene-ether (49 : 1) (250 ml.)	pale yellow solid (1.17 g.)

The pale yellow solid (327 mg.) is crystallised from ethanol (8 ml.) to give 13 - ethyl-3,17 - diacetoxygona - 1,3,5(10),9(11),16 - pentaene (250 mg.), m.p. 150—1°C. (Found: C, 75.41; H, 7.19%; $C_{23}H_{26}O_4$ requires C, 75.38; H, 7.15%).

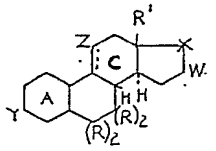
Diborane [generated by adding sodium borohydride (1.24 g.) in diglyme (30 ml.) to boron trifluoride etherate (10 ml.) in diglyme (20 ml.) over a period of 2 hours] is added to 13 - ethyl - 3,17β - diacetoxy - gona - 1,3,5(10), 9(11), 16 - pentaene - 3,17β-diol in dry tetrahydrofuran (150 ml.). Water 20 ml. is added cautiously to decompose the excess diborane and the resulting homogeneous solution is treated with hydrogen peroxide (100 volume: 30 ml.) and 2 *N* sodium hydroxide (42 ml.). After refluxing for ½ hour, the tetrahydrofuran is evaporated *in vacuo;* the resulting aqueous solution is acidified with concentrated hydrochloric acid (10 ml.) and extracted with ethyl acetate (3 × 10 ml.). The extracts are washed with aqueous potassium bicarbonate and brine, dried and evaporated *in vacuo* to obtain a solid which is triturated with hot acetone, cooled, and filtered to obtain crude product (1.09 g.), m.p. 249—54°d; 449 mg. of the latter is recrystallised from ethanol (10 ml.) to obtain 13-ethylgona-1,3,5(10) - triene-3,11α,16α,17β-tetrol (299 mg.), m.p. 256—8°C. Found: C, 71.79; H, 8.14%. Analysis calculated for $C_{19}H_{26}O_4$. C, 71.67; H, 8.23%.

EXAMPLE 21

13 - Ethylgona - 1,3,5(10) - triene - 3,11α,16α,17β - tetrol (154 mg.) in acetic anhydride (3 ml.) and pyridine (3 ml.) is heated at 180° for 1½ hr. The solvents are evaporated *in vacuo* to give 13 - ethyl - 3,11α,16α,17β - tetra - acetoxygona - 1,3,5(10)-triene, m.p. 104°C. Found: C, 66.72; H, 6.98%. Calculated for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04%.

WHAT I CLAIM IS:—

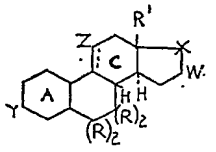
1. A 13 - (C_{2-5})alkyl - 3,11,17 - trioxygenated - unsaturated gonane having the structure (I)

I 

where R^1 is a C_{2-5} alkyl group, X is a carbonyl, hydroxymethylene or esterified hydroxymethylene group, Z is an oxo, hydroxy, ketalised oxo, or etherified or esterified hydroxy group, W is hydrogen, a hydroxy group or an esterified hydroxy group, R is hydrogen or one or more C_{1-6} alkyl groups at one or both of positions 6 and 7 (which may be the same or different) and Y is a hydroxy or esterified or etherified hydroxy group and ring A is aromatic or Y is an etherified hydroxy group and ring A contains the 2,5(10) - diene system or Y is an oxo group and ring A contains a 4 or 5(10) double bond; and ring C can be saturated in which case the hydrogen atom at the 9-position is in the α-configuration or it can contain a 9(11) double bond when Z is an acyloxy group; or a D-homo analogue thereof.

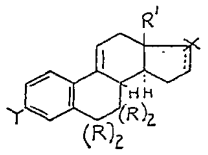
2. A compound according to Claim 1, where Z is a benzoyloxy group.
3. A compound according to Claim 1, where Z is an alkanoyloxy group.
4. A compound according to Claim 3, where the alkanoyloxy group is an acetoxy group.
5. A compound according to any one of Claims 1 to 4, where Z is an α - hydroxy or α - acyloxy group.
6. A compound according to any one of Claims 1 to 4, where Z is a β - hydroxy or β - acyloxy group.
7. A compound according to any one of Claims 1 to 6, where X is a benzoyloxymethylene group.
8. A compound according to any one of Claims 1 to 6, where X is an alkanoyloxymethylene group.
9. A compound according to Claim 8, where the alkanoyloxymethylene group is an acetoxymethylene group.
10. A compound according to any one of Claims 1 to 9, where Y is an acetoxy, benzoyloxy or methoxy group.
11. A compound according to any one of Claims 1 to 10, in which W is an acetoxy group.
12. A compound according to any one of Claims 1 to 11, where when W is an acyloxy or hydroxy group, then it is in the α-configuration.
13. A compound according to any one of Claims 1 to 12 wherein R^1 is ethyl, propyl, isopropyl, butyl or pentyl.
14. 13 - Ethylgona - 1,3,5(10) - triene - 3,11α,17β - triol.
15. 13 - Ethyl - 3,11α,17β - triacetoxygona - 1,3,5(10) - triene.
16. 13 - Ethyl - 3,11α,17β - tribenzoyloxygona - 1,3,5(10) - triene.
17. 13 - Ethyl - 3 - benzoyloxygona - 1,3,5(10) - triene - 11α,17β - diol.
18. 13 - Ethyl - 3 - benzoyloxygona - 1,3,5(10) - triene - 11,17 - dione.
19. 13 - Ethyl - 3 - benzoyloxy - 11 - acetoxygona - 1,3,5(10),9(11) - tetraen - 17 - one.
20. 13 - Ethylgona - 1,3,5(10) - triene - 3,11β,17β - triol.
21. 13 - Ethyl - 3 - methoxygona - 1,35(10) - triene - 11α,17β - diol.
22. 13 - Ethyl - 11β,17β - dihydroxygon - 4 - en - 3 - one.
23. 13 - Ethyl - 3 - methoxy - 11α,17β - diacetoxygona - 1,3,5(10) - triene.
24. 13 - Ethyl - 3 - methoxygona - 2,5(10) - diene - 11α,17β - diol.
25. 13 - Ethyl - 11α,17β - dihydroxygon - 4 - en - 3 - one.
26. 13 - Ethylgon - 4 - ene - 3,11,17 - trione.
27. 13 - Ethyl - 11α,17β - dihydroxygon - 5(10) - en - 3 - one.
28. 13 - Ethylgona - 1,3,5(10) - triene - 3,11α,16α,17β - tetrol.
29. 13 - Ethyl - 3,11α,16α,17β - tetra - acetoxygona - 1,3,5(10) - triene.
30. 13 - Ethyl - 3 - methoxygona - 1,3,5(10) - triene - 11,17 - dione.
31. 13 - Ethyl - 3 - methoxygona - 1,3,5(10) - triene - 11β,17β - diol.
32. 13 - Ethyl - 3 - methoxygona - 2,5(10) - diene - 11β,17β - diol.
33. 13 - Ethyl - 3 - methoxygona - 2,5(10) - diene - 11,17 - dione.
34. The 17 - ketal of a compound according to any one of claims 1 to 6, 18, 19, 30 or 33.
35. The 3 - hydroxy and 3 - ester derivatives of the compounds according to any one of claims 1 to 9, 11 to 13, 22, 25 or 27, where ring A contains a 4 or 5(10) double bond.
36. A compound according to claim 1, substantially as herein described and shown with reference to any one of Examples 1 to 19, 20 and 21.
37. A process for making a compound of structure (I)

I



where R^1 is a C_{2-5} alkyl group, X is a carbonyl, hydroxymethylene or esteried hydroxymethylene group, Z is an oxo, hydroxy, ketalised oxo, or etherified or esterified hydroxy group, W is hydrogen, a hydroxy group or an esterified hydroxy group, R is hydrogen or one or more C_{1-6} alkyl groups at one or both of positions 6 and 7 (which may be the same or different) and Y is a hydroxy or esterified or etherified hydroxy group

and ring A is aromatic or Y is an etherified hydroxy group and ring A contains the 2,5(10) - diene system or Y is an oxo group and ring A contains a 4 or 5(10) double bond; and ring C can be saturated in which case the hydrogen atom at the 9-position is in the α-configuration or it can contain a 9(11) double bond when Z is an acyloxy group; or a D-homo analogue thereof in which a compound of structure (II)

II 

where R, R^1 and X are as defined above, Y is a hydroxy or etherified or esterified hydroxy group and there can be an ethylenic bond at the 16-position in the D-ring, or the D-homo analogue of structure II is subjected to hydroboration, and if desired

(i) the product of hydroboration is Birch reduced to give a 2,5(10)-diene,

(ii) the Birch reduction product is hydrolysed to give a compound where ring A has a 4 or 5(10) double bond and a 3 - keto group,

(iii) an 11- or 16- or 17 - hydroxy group is oxidised to a corresponding keto group,

(iv) an 11-keto group is reduced to an 11β-hydroxy group or is ketalized, or

(v) an 11- or 16- or 17-hydroxy group is esterified.

38. A process according to claim 37 in which the hydroboration is achieved by the use of diborane followed by hydrogen peroxide in the presence of alkali.

39. A process according to claim 37 or claim 38 in which the compound of structure (II) where ring D has a 16(17)-double bond and X is an acyloxymethylene group is prepared by subjecting a gona - 1,3,5(10),9(11) - tetraen - 17 - one to enol acylation.

40. A process according to claim 39 in which the enol acylation is achieved by the use of isopropenyl acetate.

41. A process according to claim 37 or 38 in which the product is subsequently totally or partially esterified.

42. A process according to claim 37 or 38 in which an 11,17 - dihydroxy product is oxidised to give an 11,17 - dione.

43. A process according to claim 42 in which the product is subsequently reduced to give an 11β,17 - diol.

44. A process according to claim 43 in which the reduction is achieved by the use of sodium borohydride.

45. A process according to any one of claims 37 to 44 in which the product where Y is an alkoxy group, Z is a hydroxy, oxo or acyloxy group, W is hydrogen or an α-hydroxy or -acyloxy group and X is a carbonyl, hydroxymethylene or acyloxymethylene group, is subjected to Birch reduction to give the corresponding 3 - alkoxy - 11,17 - dihydroxygona - 2,5(10) - diene having also a 16α - hydroxy group in the case where there was a substituent at the 16-position and if desired, the Birch reduction product is hydrolysed under vigorous or mild acid conditions to give the corresponding gon-4 or 5(10) - en - 3 - one respectively.

46. A process according to claim 45 in which the product, a 3 - alkoxy - 11,17-dihydroxygona - 2,5(10) - diene optionally having also a 16α - hydroxy group, is oxidised to convert the free hydroxy groups to carbonyl groups.

47. A process according to claim 42 or claim 46 in which an 11,17 - dione oxidation product is enol acylated to give the corresponding 11 - acyloxygona - 1,3,5(10), 9(11) - tetraen - 17 - one.

48. A process according to claim 47 in which the enol acylation is achieved by the use of acetic anhydride in the presence of pyridine.

49. A process according to claim 37, substantially as described herein and shown with reference to any one of Examples 1, 9 and 20,.

50. A process according to claim 41, substantially as described herein and shown with reference to any one of Examples 2 to 4, 8, 15 and 21.

51. A process according to claim 42, substantially as described herein and shown with reference to Examples 5, 10, 14 or 18.

52. A process according to claim 43, substantially as described herein and shown with reference to Example 7 or Example 11.

53. A process according to claim 45, substantially as described herein and shown with reference to any one of Examples 12, 13, 16, 17 and 19.

54. A process according to claim 47, substantially as described herein and shown with reference to Example 6.

55. A 13 - (C_{2-5}) alkyl - 3,11,17 - trioxygenated - unsaturated gonone as claimed in claim 1 whenever prepared by the process according to any one of claims 37 to 54, or its obvious chemical equivalent.

56. A pharmaceutical composition comprising a steroid compound according to any one of claims 1 to 33, 36 and 55 in association with a pharmaceutically acceptable carrier.

57. A pharmaceutical composition comprising a steroid compound according either to claim 34 or 35 in association with a pharmaceutically acceptable carrier.

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